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TO:

Editor in Chief of Minerva Anestesiologica

Modena, 3 October, 2016

Dear Dr Cavaliere,

As kindly requested we shortened the text by about 150 words (around 15%), simplified some concepts and revised grammar and bibliography.

We thank you again for the opportunity given

.

Yours Sincerely,

Dr. Massimo Girardis

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Injury-induced immunosuppression: we are finally on the right track?

Stefano Busani, Andrea Cossarizza* and Massimo Girardis

Intensive Care Unit and *Chair of Pathology and Immunology, University of Modena and Reggio Emilia, Modena, Italy

In critically ill patients multiple stress events such as infection, trauma, surgery and burn may lead to dysregulation of the immune response with an excessive pro-inflammatory phase and/or a prolonged and profound dysfunction in immune response. This latter, called immune-paralysis, predisposes patient to secondary life-threatening infections and seems to be crucial for long-term outcomes in patients surviving to first hit [1]. Moreover, due to impairment in the innate and adaptive immunity, antibiotic therapy alone may result ineffective in immunosuppressed patients. Therefore, early detection of immune dysfunction and its support by specific strategies may be the key for improving survival [2, 3].

In the last years the awareness of the pivotal role of immunity in acute illnesses has led to significant advances in the identification of biomarkers useful for the assessment of the immune system competence in critically ill patients. In the current issue of Minerva Anestesiologica, Rouget et al. [4] provided a detailed and exhaustive review of these bio-markers. The authors focused on immature granulocytes, quantitative and qualitative alterations in dendritic cells, monocytes human leucocytes antigen DR, anti-inflammatory interleukins and the recent concept of leucocyte reprogramming [5]. The role of the possible markers of immunosuppression expressed by B and/or T lymphocytes has been also reviewed

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in detail, along with a novel transcriptomic view that would allow the identification of genes that are up or down-regulated during a stressing insult.

In addition to molecules and cells described by Rouget et al. [4], further bio-markers may be helpful for identifying an hypo-reactive state of the immune system. A low plasma concentration of the different isotypes of endogenous immunoglobulins at the onset and throughout the course of sepsis has been associated to an increased risk of mortality in septic patients [6, 7]. Due to the pleiotropic effects of immunoglobulins in the inflammatory-immune response, the reasons and the true meaning of this association are still debated. However, several mechanisms by which immunoglobulins may exert anti-apoptotic effects of different immune cells populations have been identified in preclinical models. Therefore, a decreased immunoglobulin plasma levels could facilitate a boost of apoptosis that has been recognized as an important cause of major immune dysfunction during late phases of sepsis [8, 9]. Remaining on apoptosis, caspase 1 is a key component of inflammasomes that trigger a potent pro-inflammatory response, ultimately inducing a type of cell death defined "pyroptosis" [10, 11]. In addition to its role as marker of an excessive pro-inflammatory condition, persisting high level of caspase 1 could be also considered an early indicator of immune system hypo-reactivity. A further potential marker of immune dysfunction might be mucosal-associated invariant T (MAIT) cells, a population of T lymphocytes that express a semi-invariant T cell receptor. An important role of MAIT cells in the early stages of bacterial infections has been postulated [12] and a recent study showed that critically ill patients with persistent MAIT cells depletion display a high susceptibility to develop hospital acquired infections [13].

A proper evaluation of hyper or under-activation of the host immune system may provide a better comprehension of the pathobiology changes occurring in sepsis as well as in other conditions such as trauma, burn and surgery, and may finally guide to a tailored therapeutic

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approach [14]. For instance, the traditional strategy aimed to suppress the immune system by inhibition of inflammatory mediators could be helpful in patients with an overwhelming pro-inflammatory state, but may be harmful in patients with a suppressed immune response [15].

The review by Rouget et al. [4] provides a straightforward analysis on the rationale for use and the feasibility of measuring immune-competence at the bedside. Unfortunately, most of the biomarkers described requires sophisticated techniques such as flow cytometry, immunohistochemistry, cytokine ELISA arrays or RNA analysis for gene expression. Despite many of these procedures are complex and have a high cost, we believe that the evaluation of the immune response is today mandatory for a proper management of septic patients. To this aim, official guidelines or consensus conferences are urgently needed to provide clinicians with a sort of "immunoscope" to monitor critically-ill patients and treat them. The future in which specific therapies will be tailored on a sound evaluation of patient pathobiology could be around the corner.

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Conflicts of interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Injury-induced immunosuppression: we are finally on the right track?

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In critically ill patients multiple stress events such as infection, trauma, surgery and burn may lead to dysregulation of the immune response with an excessive pro-inflammatory phase and/or a prolonged and profound dysfunction in immune response. This latter, called immune-paralysis, predisposes patient to secondary life-threatening infections and seems to be crucial for long-term outcomes in patients surviving to first hit [1]. Moreover, due to impairment in the innate and adaptive immunity, antibiotic therapy alone may result ineffective in immunosuppressed patients. Therefore, early detection of immune dysfunction and its support by specific strategies may be the key for improving survival [2, 3].

In the last years the awareness of the pivotal role of immunity in acute illnesses has led to significant advances in the identification of biomarkers useful for the assessment of the immune system competence in critically ill patients. In the current issue of Minerva Anestesiologica, Rouget et al. [4] provided a detailed and exhaustive review of these bio-markers. The authors focused on immature granulocytes, quantitative and qualitative alterations in dendritic cells, monocytes human leucocytes antigen DR, anti-inflammatory interleukins and the recent concept of leucocyte reprogramming [5]. The role of the possible markers of immunosuppression expressed by B and/or T lymphocytes has been also reviewed in detail, along with a novel transcriptomic view that would allow the identification of genes that are up or down-regulated during a stressing insult.

In addition to molecules and cells described by Rouget et al. [4], further bio-markers may be helpful for identifying an hypo-reactive state of the immune system. A low plasma concentration of the different isotypes of endogenous immunoglobulins at the onset and throughout the course of sepsis has been associated to an increased risk of mortality in septic patients [6, 7]. Due to the pleiotropic effects of immunoglobulins in the inflammatory-immune response, the reasons and the true meaning of this association are still debated. However, several mechanisms by which immunoglobulins may exert anti-apoptotic effects of different immune cells populations have been identified in preclinical models. Therefore, a decreased immunoglobulin plasma levels could facilitate a boost of apoptosis that has been recognized as an important cause of major immune dysfunction during late phases of sepsis [8, 9]. Remaining on apoptosis, caspase 1 is a key component of inflammasomes that trigger a potent pro-inflammatory response, ultimately inducing a type of cell death defined "pyroptosis" [10, 11]. in addition to its role as marker of an excessive pro-inflammatory condition, persisting high level of caspase 1 could be also considered an early indicator of immune system hypo-reactivity. A further potential marker of immune dysfunction might be mucosal-associated invariant T (MAIT) cells, a population of T lymphocytes that express a semi-invariant T cell receptor. An important role of MAIT cells in the early stages of bacterial infections has been postulated [12] and a recent study showed that critically ill patients with persistent MAIT cells depletion display a high susceptibility to develop hospital acquired infections [13].

A proper evaluation of hyper or under-activation of the host immune system may provide a better comprehension of the pathobiology changes occurring in sepsis as well as in other conditions such as trauma, burn and surgery, and may finally guide to a tailored therapeutic approach [14]. For instance, the traditional strategy aimed to suppress the immune system by

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inhibition of inflammatory mediators could be helpful in patients with an overwhelming pro-inflammatory state, but may be harmful in patients with a suppressed immune response [15].

The review by Rouget et al. [4] provides a straightforward analysis on the rationale for use and the feasibility of measuring immune-competence at the bedside. Unfortunately, most of the biomarkers described requires sophisticated techniques such as flow cytometry, immunohistochemistry, cytokine ELISA arrays or RNA analysis for gene expression. Despite many of these procedures are complex and have a high cost, we believe that the evaluation of the immune response is today mandatory for a proper management of septic patients. To this aim, official guidelines or consensus conferences are urgently needed to provide clinicians with a sort of "immunoscope" to monitor critically-ill patients and treat them. The future in which specific therapies will be tailored on a sound evaluation of patient pathobiology could be around the corner.

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